REMARKS

Specification Amendment

The specification has been amended to address the Office's objection to the specification for containing hyperlinks. Specifically, the specification has been amended to delete a citation to a website on page six.

No new matter has been added by way of this amendment.

Claim Amendments

Claims 1-25 are pending in this application. With the present submission, claims 2, 12, 14, 18, 19, and 21 have been cancelled without prejudice or disclaimer. Claims 1, 3, 6, 16, and 17 have been amended.

Specifically, claim 1 has been amended to recite: "[a] method of identifying a candidate p21 pathway modulating agent, said method comprising the steps of: (a) providing an assay system capable of detecting CSNK1G expression and/or activity comprising cultured cells that express a CSNK1G polypeptide or nucleic acid; (b) contacting the assay system with a candidate test agent; and (c) determining the expression or activity of CSNK1G in the assay system, wherein a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent. Amended claim 1 finds support in the as-filed application at, *inter alia*, page 2, lines 26-31.

Claim 3 has been amended merely to correct the dependency.

Claim 6 has been amended merely to delete reference to the non-elected inventions.

Claim 16 has been amended to recite: "[t]he method of Claim 1, comprising the additional steps of: (d) providing a second assay system capable of detecting a change in the p21 pathway comprising cultured cells that express a CSNK1G polypeptide or nucleic acid; (e) contacting the second assay system with the candidate test agent of (b) or an agent derived therefrom; and (f) determining a change in the p21 pathway in the second assay system, wherein a as a candidate p21 modulating agent. Amended claim 16

finds support in the as-filed application at, *inter alia*, page 21, line 32 to page 22, line 2 and pages 29-32.

Claim 17 has been amended merely to provide proper antecedent basis.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice or disclaimer, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. Additionally, these amendments and cancellation are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. No new matter has been added by way of these amendments. Accordingly, Applicants respectfully request the entry of the amendments presented.

Oath/Declaration

The Oath is objected to because the change of address for Haiguang Zang in the Oath/Declaration received February 4, 2005 is not initialed or dated. The Office states that it "will not consider whether noninitialed and/or nondated alterations were made before or after signing of the Oath or Declaration but will require a new Oath or Declaration (37 CFR 1.64)." (Office Action, page 2).

Applicants respectfully submit that a new Oath or Declaration is not required. Under 37 CFR 1.67(3), deficiencies or inaccuracies due to the failure to meet the requirements of 37 CFR 1.63(c) (i.e., correction of the mailing address of an inventor) in an Oath or Declaration may be corrected with an application data sheet in accordance with 37 CFR 1.76. (see 37 CFR 1.67(3), 37 CFR 1.63(c)(1), and 37 CFR 1.76). Applicants submit herewith an application data sheet containing the current address for inventor Haiguang Zang.

Information Disclosure Statement

The Office alleged that parts of the Information Disclosure Statement filed on March 24, 2005 fail to comply with 37 CFR 1.98(a)(1). Specifically, the Office alleged

that citations 1-16 fail to provide a publication date. Applicant will file a supplemental Information Disclosure Statement at a future date to include the publication dates of citations 1-16.

Objection to the Specification

The specification was objected to for containing hyperlinks. The specification has been amended to address this objection. Applicant respectfully requests withdrawal of the objection to the specification.

Claim Objections

Claims 1-3, 6, 16, and 17 were objected to for allegedly reciting non-elected subject matter. The claims have been amended to address this objection. Applicant respectfully requests withdrawal of the claim objections.

35 USC § 112, Second Paragraph Rejections

Claims 1-3, 6, 16, and 17 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 2 has been cancelled, rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claims 1, 3, 6, 16, and 17.

The Office alleged that the phrase "agent-biased activity" renders claims 1 and 16, and dependent claims 2, 3, 6, and 17, indefinite. Claims 1 and 6 have been amended to remove the phrase "agent-biased activity", thus rendering the rejections moot. Applicants respectfully request withdrawal of these rejections.

In addition, the Office alleged that the phrase "the system" in claims 1 (line 5) and 16 (line 6) lack antecedent basis and thus renders the claims indefinite. Dependent claims 2, 3, 6, and 17, as dependent from claim 1 and/or claim 16, were rejected as allegedly being indefinite for the same reasons. Claims 1 and 16 have been amended to provide proper antecedent basis, thus obviating the rejections. Applicants respectfully request withdrawal of these rejections.

The Office further alleged that the phrase "a secondary assay system" in claim 16 renders the claim indefinite. Specifically, the Office states that it is unclear whether the second assay system must consist of the same or different steps from those used in the first assay system or may consist of the same or different steps of the from those used in the first assay system. Applicants submit that claim 16 has been amended to clarify the steps of the second assay system and that the steps are now clear and definite. The claim does not require the second assay to consist of the same steps as the first assay, nor does the claim require the second assay to consist of different steps from the first assay. Thus, one skilled in the art would realize that the steps of the second assay may consist of the same or different steps from those of the first assay. Regardless, as amended, the steps of the second assay are clear and definite on their face. Accordingly, Applicants respectfully request withdrawal of this rejection.

35 USC § 112, First Paragraph, Rejections

Enablement

Claims 1-3, 6, 16 and 17 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claim 2 has been cancelled, rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claims 1, 3, 6, 16, and 17.

The Office Action alleged that although the specification is enabling for a method of determining the effect of reducing the expression of the proteins set forth by SEQ ID NOs: 1, 8, and 11 on cell proliferation, the specification does not reasonably provide enablement for a method of identifying a p21-pathway modulator by testing the effect any compound in any assay system comprising any CSNK1G. The Office alleged that the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the instant claims.

Applicants submit that the instant claims, directed to assays for screening for a candidate p21 pathway modulating agent using an assay system comprising cultured cells that express CSNK1G polypeptide or nucleic acid, contacting the assay system with a

candidate test agent, and determining a change in CSNK1G expression or activity between the presence and absence of said candidate test agent so as to indicate the presence of a p21 pathway modulating agent, is fully enabled by the instant specification.

Under 35 U.S.C. §112, all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. In re Wands, 858 F.2d 731 (Fed. Cir. 1988); United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. With regard to the second part of the test, one must bear in mind that "a patent need not teach, and preferably omits, what is well known in the art." Hybritech v. Monoclonal Antibodies, 802 F.2d 1367, 1384 (Fed.Cir.1986). Further, the Federal Circuit has explained that "[t]he key word is 'undue' and not 'experimentation'. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also *Massachusetts Institute of Technology vs. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

Contrary to the Office's allegation, the instant specification provides considerable guidance to enable a skilled artisan to make and use the claimed screening assays. Initially, the specification teaches that CSNK1G polypeptides and the p21 pathway are involved in the biological processes relating to cell cycle regulation and cell growth (specification, page 1). The specification also directly teaches that CSNK1G polypeptides are serine/threonine kinases involved in the regulation of cell growth (specification at page 1, lines 18-24).

In addition, the specification describes in detail the characteristics of CSNK1G polynucleotides and polypeptides and further provides representative examples of specific CSNK1G polypeptides and polynucleotides that can be used in the assay systems, as well as providing their sequences. See specification at page 4, line 9 to page 5, line 5 (CSNK1G polypeptides) and page 5, line 6 to page 7, line 25 (CSNK1G polynucleotides). The specification further provides methods for isolating and producing CSNK1G polynucleotides and polypeptides at pages 7-9.

In addition, the specification describes agents that modulate the function of CSNK1G and/or the p21 pathway and further teaches that a candidate test agent can include CSNK1G related proteins, CSNK1G-specific antibodies, CSNK1G-specific antisense oligomers and other nucleic acid modulators, and chemical agents that specifically bind to or interact with CSNK1G, or compete with a CSNK1G binding partner (specification at 2, line 22 to page 3, line 2; page 3, lines 14-19; pages 12-13), and provides several specific examples of such agents (specification at pages 13-14 (small molecule modulating agents), pages 14-17 (protein modulating agents), and pages 17-19 (nucleic acid modulating agents).

Furthermore, the specification teaches that the assay system can be a cell-based assay (specification at page 2, lines 26-31) and provides examples of cell-based assay systems that can be used to determine whether the candidate test agent has altered the expression or activity of CSNK1G. For example, the specification teaches that a change in the expression of CSNK1G can be determined using western blotting, immunoprecipitation, and immunohistochemical analyses to determine protein levels, as well as Taqman, RT-PCR, Northern blotting, and other analyses to determine mRNA levels (pages 37-38). The specification teaches that a change in the activity of CSNK1G can be determined using kinase assays, such as the kinase assay described on pages 36-37, as well as other kinase assays well-known in the art.

In addition, the specification provides examples of functional assay systems to determine the effect of the candidate test agent that changes the expression or activity of CSNK1G, such as cell proliferation and cell cycle assays, kinase assays, apoptosis assays, hypoxic induction assays, angiogenesis assays, antibody-based assays, cell adhesion

assays, tubulogenesis assays, cell migration assays, and sprouting assays, among others. (specification at page 3, lines 3-5; page 21, line 25 to page 29).

In addition, the specification provides numerous examples of assay systems that can be used to confirm that the test agent modulates the p21 pathway. (specification at pages 29-32).

Applicants submit that, based on the discussions presented above, there is ample support for the specification being enabling. Applicants assert that, using the guidance provided in the specification, one skilled in the art would be able to make and use the claimed screening assays. For the reasons set forth above, the claims are fully enabled and can be readily practiced by one skilled in the art. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, first paragraph, rejection.

Written Description

Claims 1-3, 6, 16, and 17 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with written description requirement. Claim 2 has been cancelled, rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claims 1, 3, 6, 16, and 17.

Specifically, the Office alleges that claims 1-3, 6, 16 and 17 are directed to a genus of methods for identifying p21 pathway modulators by testing the effect of any compound in any assay system or any cell culture assay system comprising any CSNK1G. The Office asserts that the specification teaches no such methods and given the lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such clear and concise terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

In order to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., id.*, at 1116; M.P.E.P § 2163(I). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A.

1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Possession can be shown "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. § 2163.02 (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; (5) and the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of <u>any</u> combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient to satisfy the written description requirement. *Id*; *see Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406. Correspondingly, the Patent Office's internal guidelines state that "the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function." M.P.E.P. § 2163(II)(A)(3)(a)(i)(C)(2).

Moreover, that which is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. M.P.E.P. § 2163 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Further, the written description requirement does not require an actual reduction to practice. M.P.E.P. § 2163.

Accordingly, an Applicant need not show that the invention will work for its intended purpose to satisfy the written description requirement.

Contrary to the Office's allegation, the specification thoroughly describes a method of identifying a candidate p21 pathway modulating agent using cultured cells that express a CSNK1G polypeptide or nucleic acid and determining the expression or activity of CSNK1G in the assay system, wherein a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent.

The Office alleges that the specification does not provide examples of assay methods that can be used to identify a candidate p21 pathway modulating agent. However, as discussed in detail above, the specification provides numerous examples of different types of assays that can be employed in the claimed methods and describes the methodology of these assays in detail. Furthermore, as discussed above, the specification thoroughly describes the characteristics of the CSNK1G polynucleotides and polypeptides used in the assays and provides numerous representative examples of both, including a description of their sequences/structures. Finally, the specification teaches the physical and chemical properties of various modulating agents including, for example, proteins, antibodies, chemical agents, nucleic acid modulators, and small molecule agents. Rather than repeat the specific support here, Applicants refer to the support outlined in the discussion of enablement.

Contrary to the Office's contention, the specification provides detailed description and numerous examples of assays, modulating agents, and CSNK1G polypeptides and polynucleotides that can be used in the claimed methods. Thus, the instant application fulfills the written description requirement under 35 U.S.C. § 112, first paragraph and Applicants respectfully requests withdrawal of the rejections.

35 USC § 102 Rejection

Claims 1 and 2 were rejected under 35 USC 102(b) as being allegedly anticipated by Beyaert et al. (1995). Claim 2 has been cancelled, rendering the rejection moot with

respect to this claim. Applicants respectfully traverse the rejection with respect to claim 1.

Beyaert et al. fails to anticipate the claimed invention. A claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. M.P.E.P. §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226 (Fed. Cir. 1989); M.P.E.P. §2131. Furthermore, the prior art reference must provide an enabling disclosure. M.P.E.P. §2121.01; *In re Hoeksema*, 399 F.2d 269 (CCPA 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention' 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ."). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. M.P.E.P. §2121.01

Claim 1 as amended is directed to a method of identifying a candidate p21 pathway modulating agent using an assay system comprising cultured cells that express a CSNK1G polypeptide or nucleic acid, contacting the assay system with a candidate test agent, and determining the expression or activity of CSNK1G in the assay system, where a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent.

The Office argued that Beyaert anticipates claim 1 because it allegedly teaches that CK1-7, a cell-permeable inhibitor of casein kinase I, reduces the phosphorylation and activity of the p75 TNF receptor and enhances apoptosis in a cellular assay system. However, the claims are directed to a method of identifying a candidate p21 pathway modulating agent. Beyaert fails to even mention p21 protein or the p21 pathway and thus fails to contemplate any association between casein kinase I and p21, and certainly fails to contemplate using an assay system comprising cells that express a CSNK1G polypeptide or nucleic acid to indicate the presence of a candidate p21 pathway modulating agent.

Furthermore, the teaching of Beyaert is limited to the study of cell apoptosis, which is a specific biological process known as "programmed cell death". Apoptosis is a biological pathway or process which actively results in the destruction of cells. This active process of cell death is distinct from and should not be confused with a down-

regulation or inhibition of cell growth. As taught in the instant specification, p21 is associated with cell-cycle regulation, i.e., the regulation of cell growth (and not the regulation of programmed cell death). The fact that Beyaert only considers casein kinase I in the context of regulating programmed cell death and fails to teach any association whatsoever of casein kinase I with the regulation of cell growth, is further evidence that Beyaert failed to contemplate a method of identifying a candidate p21 pathway modulating agent, i.e., an agent involved in the regulation of cell growth.

Beyaert et al. fails to mention the p21 pathway or the modulation of a p21 pathway and thus fails to teach or suggest a method for identifying a candidate p21 pathway modulating agent using an assay system comprising cultured cells that express a CSNK1G polypeptide or nucleic acid. Thus, Beyaert et al. fails to anticipate the claimed invention because it fails to teach each and every element as set forth in claim 1 and fails to describe the identical invention in as complete detail as is contained in the claim. Accordingly, Applicants respectfully request withdrawal of the 35 USC 102(b) rejection in view of Beyaert et al.

35 USC § 103 Rejections

Claims 1, 2, 6, 16, and 17 were rejected under 35 USC 103(a) as being allegedly obvious over Beyaert et al. (1995) in view of Gehr et al. 1992. Claim 2 has been cancelled, rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claims 1, 6, 16, and 17.

The Office alleges that Beyaert et al teach that CKI-7, an inhibitor of casein kinase I, reduces the phosphorylation and activity of the p75 TNF receptor and enhances apoptosis in a cellular assay system. The Office admits that Beyaert et al do not teach a method for testing the effect of CKI-7 (casein kinase inhibitor) on cell proliferation in a secondary assay system. The Office alleges that Gehr et al teach that the p75 TNF receptor mediates proliferation in peripheral blood mononuclear cells (PBMCs). The Office concluded that it would have been obvious to a person of ordinary skill in the art to test the effect of the CKI-7 casein kinase inhibitor taught by Beyaert in the PBMC proliferation assay of Gehr, as one would have allegedly been motivated from a desire to determine whether casein kinase I modulates the effect of the p75 TNF receptor on proliferation. The Office further stated that

the expectation of success is high, as Beyaert teaches methods for treating intact cells with CKI-7 and Gehr teaches methods for detecting proliferation in PBMCs.

Under *Graham v. John Deere* (383 U.S. 1 (1966)) factual inquires to be made in determining obviousness are: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art. Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings and there must be a reasonable expectation of success in arriving at the claimed invention.

The Supreme Court of the United States recently addressed the legal standard for determining obviousness under 35 U.S.C. § 103 in *KSR International. Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). At the outset, reaffirming the objective standard for obviousness set forth in *Graham v. John Deere Co. of Kansas City,* (383 U.S. 1, 17-18 (1966)), the KSR Court held that the teaching-suggestion-motivation test ("the TSM test") previously devised by the Federal Circuit, if not applied in a rigid and mandatory formula, is consistent with the *Graham* analysis. *KSR,* at 1731. Thus, the TSM test framework is still valid post *KSR*.

Applicants respectfully submit that, in its obviousness rejection based on the combined teachings of Beyhaert and Gehr, the Office has overlooked the inventive aspect of the claimed method of identifying a candidate p21 pathway modulating agent using an assay system that detects a change in CSNK1G expression or activity. As explained herein, neither Beyhaert nor Gehr even considers the possibility that an assay capable of detecting a change in CSNK1G expression or activity could be used to screen for a candidate p21 pathway modulating agent. As previously discussed, Beyaert fails to mention p21 protein or the p21 pathway and thus fails to contemplate any association between casein kinase I and p21, and certainly fails to contemplate using an assay system comprising cells that express a CSNK1G polypeptide or nucleic acid to indicate the presence of a candidate p21 pathway modulating agent. Gehr merely studied the functional roles of the two TNF receptors (α and β) by blocking the different receptors with antibodies and determining the effect on cell proliferation of PBMCs. Gehr makes

no mention whatsoever of casein kinase or p21. In fact, Gehr relates exclusively to the study TNF and has nothing whatsoever to do with casein kinase or p21. As such, its teaching merely serves to provide a cell proliferation assay. However, cell proliferation assays, such as the one described in Gehr, were known in the art and are not the inventive aspect of the invention.

The Office merely makes a conclusory statement that one would have been motivated to combine the teachings of Beyhaert and Gehr to determine if a casein kinase I inhibitor modulates the effect of the p75 TNF receptor on proliferation. However, given that Beyhaert is only concerned with the role of TNF in the apoptosis process and Gert fails to even mention casein kinase I or inhibitors thereof and is concerned exclusively with the role of TNF in cell proliferation, Applicants submit that one would not have been sufficiently motivated to combine the teachings of these references as they hardly seem relevant to one another.

Furthermore, even if for the sake of argument, one were to combine the teachings of these references, the combination would not have led one to successfully arrive at the presently claimed methods. Neither Beyhaert nor Gehr even mentions p21, much less describes the function of p21 or the p21 pathway. Furthermore, Gehr doesn't mention casein kinase at all and neither Beyhaert nor Gehr provides any teaching or suggestion whatsoever that there may be an association or connection between casein kinase (CSNK1G) expression or activity and p21. However, this association is the crux of the invention. In the absence of any teaching or suggestion whatsoever of an association between CSNK1G and p21, one simply would not have arrived at a method of identifying a candidate p21 pathway modulating agent using as assay system that detects a change in CSNK1G expression or activity.

For the reasons set forth above, the teachings of Beyaert and Gehr, alone or in combination, do not render obvious the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103(a) rejections.

Claims 1 and 2 were rejected under 35 USC 103(a) as being allegedly obvious over Yoshii et al. (2002) in view of Beyhaert et al. (1995). Claim 2 has been cancelled,

rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claim 1.

The Office alleges that Yoshii et al teach that phosphorylation of galectin-3 by casein kinase I causes an up-regulation of $p21^{WAF1/CIP1}$, as measured by Western Blotting (Figure 4). The Office admits that Yoshii et al do not teach using their western Blotting method to identify agents that inhibit galectin-3 phosphorylation by casein kinase I and thereby inhibit $p21^{WAF1/CIP1}$ expression. However, the Office argued that it would have been obvious to test the effect of the cell-permeable CK1-7 inhibitor of Beyhaert et al. in the method of Yoshi et al. because one would have been motivated to pharmacologically confirm that phosphorylation of galactin-3 by casein kinase I causes up-regulation of $p21^{WAF1}$/C1P1. The Office further stated that the expectation of success is high, as Beyaert teaches methods for treating intact cells with CKI-7 and Yoshi teaches methods for detecting galectin-3 phosphorylation and $p21^{WAF1/CIP1}$ up-regulation.

Applicants respectfully submit that one would not have been sufficiently motivated to combine the teachings of Beyhaert and Yoshii to arrive at the presently claimed invention. As previously discussed, the teachings of Beyhaert focus solely on the regulation of TGF and its role in apoptosis. Beyhaert is not concerned with the regulation of the p21 pathway and, in fact, fails to mention p21 at all. Consequently, it fails to contemplate or recognize any association between casein kinase I and the p21 pathway. As such, Beyhaert certainly fails to contemplate using cells that express a CSNK1G polypeptide or nucleic acid in an assay system to indicate the presence of a candidate p21 pathway modulating agent.

In contrast to Beyhaert, Yoshii is concerned with the regulation of an entirely different gene, galectin-3. Furthermore, while Yoshi studied the phosphorylation state of galectin-3 and its role in apoptosis and mentions that casein kinase I phosphorylates galectin-3, Yoshii is not concerned with casein kinase I or the regulation of the p21 pathway. Rather, solely in an effort to study the effects of phosphorylation on galectin-3, Yoshii designed recombinant vectors containing either wild-type galectin-3 that were capable of being phosphorylated or vectors containing mutant galectin-3 that were not capable of being phosphorylated. Yoshii showed in Figure 4 that cells containing wild-type galectin-3 expressed $p21^{WAF1/CIP1}$ and cells containing mutant galectin-3 did not

express $p21^{WAF1/CIP1}$. Thus, Yoshii does not use or even contemplate using an agent that alters the expression or activity of casein kinase I to modulate the expression of p21, much less to indicate the presence of a candidate p21 pathway modulating agent in an assay system. Instead, Yoshi designed wild-type (phosphorylated) and mutant (unphosphorylated) galectin-3 and used them in an assay system that functions independently of the level of expression or activity of casein kinase I.

Given that Beyhaert is only concerned with the role of TNF in the apoptosis process and Yoshi is only concerned with phosphorylation state of an entirely different gene, galectin-3, and its role in cell-cycle regulation, Applicants submit that one would not have been sufficiently motivated to combine the teachings of these references.

Furthermore, even if for the sake of argument, one were to combine the teachings of these references, the combination would not have led one to successfully arrive at the presently claimed methods. Neither Beyhaert nor Yoshii is concerned with the regulation of p21 or the p21 pathway and consequently neither contemplates using an agent to alter the expression or activity of casein kinase I in an effort to determine modulators of p21. Beyhaert does not provide any teaching or suggestion whatsoever that there may be an association or connection between casein kinase (CSNK1G) expression or activity and p21. While Yoshii teaches that casein kinase phosphorylates galectin-3 and that phosphorylated galectin-3 is capable of expressing p21, it is not concerned with the regulation of p21 per se and does not contemplate using an agent that alters the expression or activity of casein kinase I to modulate the expression of p21, much less to screen for the presence of a candidate p21 pathway modulating agent. In the absence of such teaching or suggestion in this regard, one simply would not have arrived at the claimed method of identifying a candidate p21 pathway modulating agent using as assay system that detects a change in CSNK1G expression or activity wherein a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent.

For the reasons set forth above, the teachings of Beyaert and Yoshii, alone or in combination, do not render obvious the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103(a) rejections.

Claims 1, 2, 3, 6, 16, and 17 were rejected under 35 USC 103(a) as being allegedly obvious over Yoshii (2002) in view of Beyaert et al. (1995) and further in view of Timchenko et al. (1996). Claim 2 has been cancelled, rendering the rejection moot with respect to this claim. Applicants respectfully traverse the rejection with respect to claims 1, 3, 6, 16, and 17.

The Office relies on Beyaert for allegedly teaching that CKI-7, an inhibitor of casein kinase I, reduces the phosphorylation and activity of the p75 TNF receptor and enhances apoptosis in a cellular assay system. The Office relies on Yoshii for allegedly teaching that that phosphorylation of galectin-3 by casein kinase I causes an up-regulation of $p21^{WAF1/CIP1}$. The Office admits that neither Yoshi, Beyaert, nor the combination thereof teach a method for testing the effect of CKI-7 (casein kinase inhibitor) on cellular proliferation in a secondary assay system. The Office alleged that Timchenko et al teach a method to demonstrate that $p21^{WAF1/CIP1}$ inhibits proliferation because it allegedly teaches that fibrosarcoma cells having defective p21 function have reduced proliferation (Figure 8). The Office concluded that it would have been obvious to a person of ordinary skill in the art to use the fibrosarcoma cells to test the effect of the CKI-7 casein kinase inhibitor taught by Beyaert in the galectin-3 phosphorylation assay of Yoshii as well as the proliferation assay Timchenko. The Office alleged that one would have been motivated from a desire to determine whether the phosphorylation of galectin-3 by casein kinase I and subsequent up-regulation of $p21^{WAF1/CIP1}$ inhibits proliferation in fibrosarcoma cells. The Office further stated that the expectation of success is high, as Beyaert teaches methods for treating intact cells with CKI-7, Yoshii teaches the phosphorylation of galectin-3 by casein kinase I causes up-regulation of $p21^{WAF1/CIP1}$ and Timchenko teaches methods for testing the role of $p21^{WAF1/CIP1}$ in the proliferation of fibrosarcoma cells.

For the reasons set forth peviously, the combined teachings of Yoshii and Beyaert do not render obvious the instantly claimed methods of method of identifying a candidate p21 pathway modulating agent using as assay system that detects a change in CSNK1G expression or activity wherein a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent.

Timchenko et al. fail to cure the deficiencies of Yoshii and Beyaert. Timchenko is concerned with yet another gene, the C/EBPα gene, and its role in growth arrest. Timchenko teaches that up-regulating the expression of the C/EBPα gene results in increased p21 expression, which, in turn, is associated with the inhibition of cell proliferation and the growth arrest of fibrosarcoma cells.

Given that Beyhaert is only concerned with the role of TNF in the apoptosis process, Yoshi is only concerned with phosphorylation state of an entirely different gene, galectin-3, and its role in cell-cycle regulation, and Timchenko is concerned only with the role of C/EBPα gene in growth arrest, Applicants submit that one would not have been sufficiently motivated to combine the teachings of these references.

Furthermore, even if for the sake of argument, one were to combine the teachings of these references, the combination would not have led one to successfully arrive at the presently claimed methods. Timchenko fails to even mention casein kinase I and thus does not provide any teaching or suggestion whatsoever that there may be an association or connection between casein kinase (CSNK1G) expression or activity and p21. Thus, like Beyaert, Timchenko fails to contemplate any association between casein kinase I and p21, and certainly fails to contemplate using an assay system comprising cells that express a CSNK1G polypeptide or nucleic acid to indicate the presence of a candidate p21 pathway modulating agent. Timchenko merely reports that an increase in the expression of C/EBPα increases p21 expression, which results in inhibition of cell proliferation. Timchenko makes no mention whatsoever of casein kinase. As such, its teaching merely serves to provide a second cell proliferation assay which is not the inventive aspect of the invention.

None of the cited references contemplates using an agent that alters the expression or activity of casein kinase I to modulate the expression of p21, much less to screen for the presence of a candidate p21 pathway modulating agent. In the absence of such teaching or suggestion in this regard, one would not have arrived at the claimed method of identifying a candidate p21 pathway modulating agent using as assay system that detects a change in CSNK1G expression or activity wherein a change in CSNK1G expression or activity between the presence and absence of said candidate test agent indicates the presence of a candidate p21 pathway modulating agent.

For the reasons set forth above, the teachings of Beyaert, Yoshii, and Timchenko, alone or in combination, do not render obvious the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103(a) rejections.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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